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Note

Synthesis of 2-(substituted aryl)-3-(N^9-carbazolylacetamidyl)-4-oxo-thiazolidines and their 5-arylidine derivatives as antifungal agents

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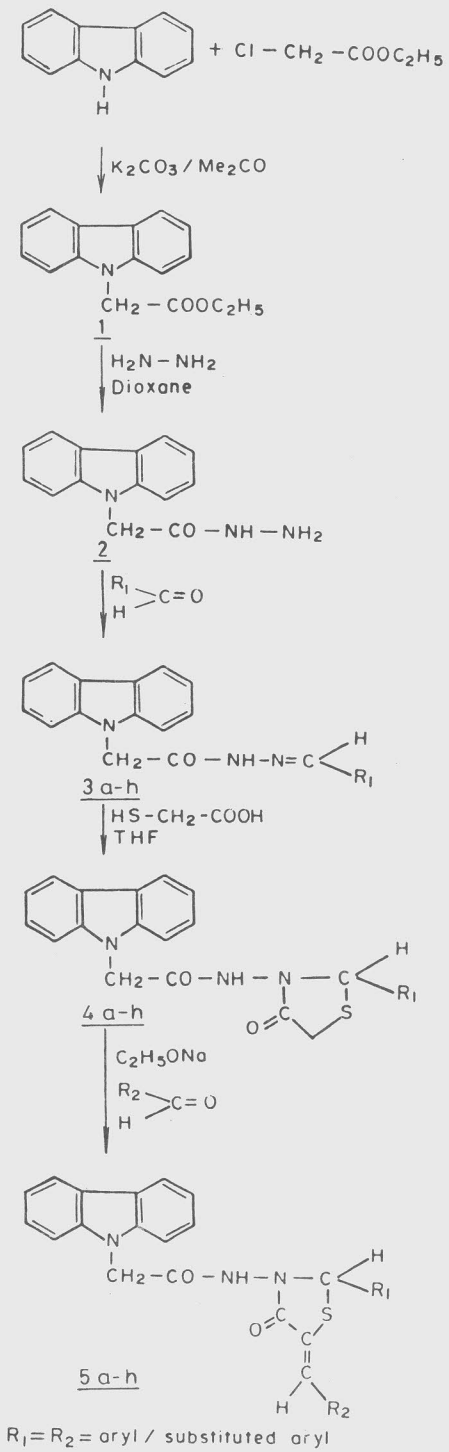
Several 2-(substituted aryl)-3-(N^9-carbazolylacetamidyl)-4-oxo-thiazolidines **4** and 2-(substituted aryl)-3-(N^9-carbazolylacetamidyl)- 5-arylidine-4-oxo-thiazolidines **5** have been synthesised and tested for their antifungal activity. Their structures have been elucidated on the basis of their elemental analyses and spectral data.

Carbazole derivatives possess potent biological activities such as antibiotic, neuroleptic, antiallergic, analgesic, anti-inflammatory, trypanocidal, insecticidal, bactericidal, fungicidal, diuretic and anticonvulsant[1-3]. We have reported earlier the synthesis and biological activity of several compounds derived from carbazole nucleus[4-6]. 4-Oxo-thiazolidines and their 5-arylidine derivatives also possess a variety of therapeutic activity[7-9]. The incorporation of 4-oxo-thiazolidine and their 5-arylidine moiety in carbazole frame work has been found to enhance the activity. Hence, in the present study the position-9 in carbazole nucleus having a secondary amine group, was used as the target for chemical modification (cf. Scheme I). The compounds have been evaluated for their antifungal activity against some selected pathogens.

Carbazole on electrophilic substitution by ethyl chloroacetate under reflux condition gave ethyl N^9-carbazolylacetate **1**. Compound **1** on amination with hydrazine hydrate afforded N^9-carbazolylacetyl hydrazine **2** which on condensation with various aromatic aldehydes yielded N^9-(phenylidine hydrazido methyl) carbazole **3**. Compound **3** on reaction with thioglycollic acid underwent dehydrative annulation to afford 2-(substituted aryl)-3-



Scheme I

Table I—Physical data of the compounds **3-5**

Compd*	R_1	R_2	Yield (%)	m.p. °C	Mol. Formula
3b	2-Cl–C_6H_4–	—	81	112-13	$C_{21}H_{16}N_3OCl$
3c	4-Cl–C_6H_4–	—	80	125-26	$C_{21}H_{16}N_3OCl$
3d	2-OCH_3–C_6H_4–	—	78	115-16	$C_{22}H_{19}N_3O_2$
3e	4-OCH_3–C_6H_4–	—	79	134-35	$C_{22}H_{19}N_3O_2$
3f	2-NO_2–C_6H_4–	—	75	117-18	$C_{21}H_{16}N_4O_3$
3g	4-NO_2–C_6H_4–	—	70	142-43	$C_{21}H_{16}N_4O_3$
3h	4-$N(CH_3)_2$–C_6H_4–	—	74	156-57	$C_{23}H_{22}N_4O$
4b	2-Cl–C_6H_4–	—	79	131-32	$C_{23}H_{18}N_3O_2SCl$
4c	4-Cl–C_6H_4–	—	76	146-47	$C_{23}H_{18}N_3O_2SCl$
4d	2-OCH_3–C_6H_4–	—	77	136-37	$C_{24}H_{21}N_3O_3S$
4e	4-OCH_3–C_6H_4–	—	72	164-65	$C_{24}H_{21}N_3O_3S$
4f	2-NO_2–C_6H_4–	—	68	133-34	$C_{23}H_{18}N_4O_4S$
4g	4-NO_2–C_6H_4–	—	66	162-63	$C_{23}H_{18}N_4O_4S$
4h	4-$N(CH_3)_2$–C_6H_4–	—	72	179-80	$C_{25}H_{24}N_4O_2S$
5b	2-Cl–C_6H_4–	2-Cl–C_6H_4–	69	162-63	$C_{30}H_{21}N_3O_2SCl_2$
5c	4-Cl–C_6H_4–	4-Cl–C_6H_4–	67	176-77	$C_{30}H_{21}N_3O_2SCl_2$
5d	2-OCH_3–C_6H_4–	2-$OCH_3C_6H_4$–	63	167-68	$C_{32}H_{27}N_3O_4S$
5e	4-OCH_3–C_6H_4–	4-O-CH_3–C_6H_4–	64	195-96	$C_{32}H_{27}N_3O_4S$
5f	2-NO_2–C_6H_4–	2-NO_2–C_6H_4–	67	165-66	$C_{30}H_{21}N_5O_6S$
5g	4-NO_2–C_6H_4–	4-NO_2–C_6H_4–	65	193-94	$C_{30}H_{21}N_5O_6S$
5h	4-$N(CH_3)_2C_6H_4$–	4-$N(CH_3)_2$–C_6H_4–	69	220-21	$C_{34}H_{33}N_5O_2S$

*All the compounds gave satisfactory C, H and N analyses.

(N^9-carbazolylacetamidyl)-4-oxo-thiazolidine **4** which on the application of Knoevenagel reaction with various aldehydes gave 2-(substituted aryl)-3-(N^9-carbazolylacetamidyl)- 5-arylidine-3-oxo-thiazolidines **5**. The structures of the products were confirmed by spectral data and elemental analyses (cf. Table I).

Antifungal Activity

The antifungal activity of the compounds **4a-h** and **5a-h** was determined by filter paper disc method[10] against the fungi *Crysosporium pannical*, *Aspergillus niger* and *Rizopus oryzae* at 100 and 500 ppm concentration using Griseofulvin as a standard drug at same concentration for comparison. The results are presented in Table II.

Experimental

Melting points were determined in an open capiliary tubes and are uncorrected. UV spectra (EtOH) were recorded on a Perkin-Elmer 202 spectrophotometer; IR spectra on an Acculab-10 spectrophotometer (ν_{max} in cm^{-1}) and ^{1}HNMR spectra on Perkin-Elmer R-32 spectrometer (90 MHz, $CDCl_3$, Chemical shifts in δ, ppm) using TMS as an internal standard.

Ethyl N^9-carbazolylacetate 1. Equimolar solution of carbazole (0.1 mole) in dry acetone (60 mL) and ethyl chloroacetate (0.1 mole) in the presence of anhydrous K_2CO_3 (5 g) was refluxed on a water-bath for about 12 hr, cooled and the solid thus obtained was filtered, dried and crystallized from ethanol to give **1**, yield 85%, m.p. 97-98° (Found: C, 75.80; H, 5.35; N, 5.51. $C_{16}H_{15}NO_2$ requires C, 75.89; H, 5.53; N, 5.53%); IR: 1730 (>C=O ester); 1460 (–N–CH_2–); ^{1}HNMR: 1.20 (t, 3H, –$COOCH_2$–CH_3), 3.60 (s, 2H, –N–CH_2–), 4.10 (q, 2H, –$COOCH_2$–CH_3), 7.20-7.90 (m, 8H, Ar-H).

N^9-Carbazole acetyl hydrazine 2. A mixture of compound **1** (0.08 mole) and hydrazine hydrate (0.08 mole) in 1,4-dioxane (50 mL) was refluxed on a water-bath for about 18 hr. It was cooled and filtered when a light brown coloured substance separated out which was crystallized from methanol to give **2**, yield 82%, m.p. 85-86° (Found: C, 70.25; H, 5.40; N, 17.52. $C_{14}H_{13}N_3O$ requires C,

Table II—Antifungal activity of the compounds **4** and **5**

Compd	*C. pannical*		*A. niger*		*B. oryzae*	
	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm
4a	+	++	–	+	–	++
4b	+	++	+	++	–	++
4c	++	+++	+	++	–	++
4d	++	+++	+	++	–	++
4e	++	+++	+	++	+	+++
4f	+	++	+	++	+	++
4g	+	++	+	++	+	++
4h	++	+++	+	++	++	+++
5a	+	++	–	+	–	++
5b	+	++	+	++	–	++
5c	+	++	+	+	–	++
5d	++	+++	++	+++	–	+++
5e	++	+++	++	+++	–	+++
5f	++	+++	+	++	–	+++
5g	+	++	+	++	++	+++
5h	++	++++	++	+++	+	+++
Gf	++	++++	++	++++	++	++++

Inhibition diameter in mm (–); <11 mm; (+), 11-14 mm; (++), 15-18 mm; (+++), 19-21 mm and (++++), 22-25 mm.
GF: Griseofulvin.

70.29; H, 5.48; N, 17.57%); IR: 3340 (–NH–NH_2), 1670 (>C=O amido); ^{1}HNMR: 2.50 (s, 2H–NH_2), 3.65 (s, 2H, –N–CH_2), 7.10-7.80 (m, 8H, Ar-H), 7.90 (s, 1H, –CONH–).

N^9-(Phenylidenehydrazido methyl)carbazole 3a. A Solution of compound **2** (0.05 mole) in $CHCl_3$ (30 mL), benzaldehyde (0.05 mole) and 4-5drops of gl. acetic acid was refluxed on a water-bath for about 8 hr, cooled and evaporated to obtain a residue which was crystallized from ethanol to give **3a**, yield 80%, m.p. 110-11° (Found: C, 77.00; H, 5.10; N, 12.79. $C_{21}H_{19}N_3O$ requires C, 77.06; H, 5.19; N, 12.84%); IR: 3330 (–NH–), 1660 (>C=O amido), 1620 (–CH=N–); ^{1}HNMR: 3.70 (s, 2H, N–CH_2), 4.40 (s, 1H, –N=NH–), 7.00-7.90 (m, 13H, Ar-H), 8.00 (s, 1H, CO–NH–).

Likewise, other N^9-arylidenehydrazidomethyl carbazoles, **3b-h** were prepared by treating **2** with various aldehydes and their physical data are given in Table I.

2-(Phenyl)-3-(N^9-carbazolylacetamidyl)-4-oxo-thiazolidine 4a. A mixture of compound **3a** (0.01 mole) in THF (25 mL) and mercaptoacetic acid (0.01 mole) with a pinch of anhydrous $ZnCl_2$ was refluxed for about 12 hr on a water-bath. The separated solid was filtered and crystallized from methanol to give **4a**, yield 78%, m.p. 148-49° (Found: C, 68.80; H, 4.70; N, 10.45. $C_{23}H_{19}N_3O_2S$ requires C, 68.82; H, 4.37; N, 10.47%); UV: 295 nm (>C=O, thiazolidinone ring); IR: 3350 (–NH–), 1710 (>C=O cyclic), 1655 (>C=O, amidyl), ^{1}HNMR: 3.20 (s, 1H, –CH–N), 3.60 (s, 2H, –CH_2S–), 3.70 (s, 2H, N–CH_2–), 7.10-7.90 (m, 13H, Ar-H), 8.60 (s, 1H, –CONH–).

Compounds **4b-h** were prepared similarly from **3b-h** and their physical data are given in Table I.

2-(Phenyl)-3-(N^9-carbazolylacetamidyl)-5-(benzylidine)-4-oxo-thiazolidine 5a. Equimolar solution of **4a** (0.005 mole) and benzaldehyde (0.005 mole) in benzene (30 mL) in the presence of C_2H_5ONa was refluxed for about 8 hr, cooled and poured into ice-cooled water. The solid thus obtained was filtered, dried and crystallized from ethanol to give **5a**: yield 72%, m.p. 184-85° (Found: C, 73.55; H, 4.65; N, 8.52. $C_{30}H_{23}N_3O_2S$ requires C, 73.61; H, 4.70; N, 8.58%); IR: 3540 (–NH–), 1715 (>C=O cyclic), 1650 (>C=O amidyl), 1630 (>C=CH–); ^{1}HNMR: 3.20 (s, 1H, –CH–N), 3.70 (s, 2H, –N–CH_2–), 5.20 (s, 1H, >C=CH–Ar), 7.10-8.00 (m, 18H, Ar-H).

Similarly, other thiazolidines, **5b-h** were prepared from **4b-h** and their physical data are given in Table I.

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